DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

0010 5 APR -1 P3:18

Dr. Rolland D. Carlson
General Manager, Divisional Vice President
Vysis, Inc.
3100 Woodcreek Dr.
Downers Grove, IL 60515

DEC 13 2004

Re: K041875
Evaluation of Automatic Class III Designation
Vysis® AutoVysion™ System
Regulation Number: 21 CFR 866.4700
Classification: Class II
Product Code: NTH

Dear Dr. Carlson:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your petition for classification of the Vysis® AutoVysion™ System that is intended for in vitro diagnostic use with the Vysis® PathVysion® HER-2 DNA Probe Kit to aid in the detection and enumeration of FISH signals in interphase nuclei, and to determine the LSI® HER-2 to CEP® 17 signal ratio of the HER-2/*neu* gene via FISH in formalin-fixed, paraffin-embedded human breast cancer tissue specimens; to reduce overall hands-on time by performing automated enumeration (for a small percentage of samples [less than 7%] manual enumeration may be required); as an adjunctive computer-assisted methodology to assist in the acquisition and measurement of images from microscope slides of formalin-fixed, paraffin-embedded breast cancer tissue sections for the presence of amplified HER-2/*neu* gene and as an aid in determining HER-2/*neu* amplification status, in conjunction with optional manual visualization directly through the fluorescence microscope.

FDA concludes that this device, and substantially equivalent devices of this generic type, should be classified into class II. This order, therefore, classifies the Vysis® AutoVysion™ System, and substantially equivalent devices of this generic type into class II under the generic name, Automated Fluorescence *in situ* Hybridization (FISH) Enumeration Systems. This order also identifies the special controls applicable to this device.

FDA identifies this generic type of device as:

21 CFR 866.4700 Automated Fluorescence *in situ* Hybridization (FISH) Enumeration Systems. An automated FISH enumeration system is a device that consists of an automated scanning microscope, image analysis system and customized software applications for FISH assays. This device is intended for in vitro diagnostic use with FISH assays as an aid in the detection, counting and classification of cells based on recognition of cellular color, size and shape and in the detection and enumeration of FISH signals in interphase nuclei of formalin-fixed, paraffin-embedded human tissue specimens.

2005N-0081

BKG 1

In accordance with section 513(f)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360c(f)(1)) (the act), devices that were not in commercial distribution prior to May 28, 1976 (the date of enactment of the Medical Device Amendments of 1976 (the amendments)), generally referred to as postamendments devices, are classified automatically by statute into class III without any FDA rulemaking process. These devices remain in class III and require premarket approval, unless and until the device is classified or reclassified into class I or II or FDA issues an order finding the device to be substantially equivalent, in accordance with section 513(i) of the act (21 U.S.C. 360c(i)), to a predicate device that does not require premarket approval. The agency determines whether new devices are substantially equivalent to previously marketed devices by means of premarket notification procedures in section 510(k) of the act (21 U.S.C. 360(k)) and Part 807 of the FDA regulations (21 CFR 807).

Section 513(f)(2) of the act provides that any person who submits a premarket notification under section 510(k) for a device may, within 30 days after receiving an order classifying the device in class III under section 513(f)(1), request FDA to classify the device under the criteria set forth in section 513(a)(1). FDA shall, within 60 days of receiving such a request classify the device. This classification shall be the initial classification of the device type. Within 30 days after the issuance of an order classifying the device, FDA must publish a notice in the **Federal Register** classifying the device type.

On October 13, 2004, FDA filed your petition requesting classification of the Vysis® AutoVysion™ System into class II. The petition was submitted under section 513(f)(2) of the act. In accordance with section 513(f)(1) of the act, FDA issued an order on October 1, 2004, automatically classifying the Vysis® AutoVysion™ System in class III, because it was not within a type of device which was introduced or delivered for introduction into interstate commerce for commercial distribution before May 28, 1976, which was subsequently reclassified into class I or class II. In order to classify the Vysis® AutoVysion™ System into class I or II, it is necessary that the proposed class have sufficient regulatory controls to provide reasonable assurance of the safety and effectiveness of the device for its intended use.

After review of the information submitted in the petition, FDA has determined that the Vysis® AutoVysion™ System, intended for in vitro diagnostic use with the Vysis® PathVysion® HER-2 DNA Probe Kit to aid in the detection and enumeration of FISH signals in interphase nuclei, and to determine the LSI® HER-2 to CEP® 17 signal ratio of the HER-2/*neu* gene via FISH in formalin-fixed, paraffin-embedded human breast cancer tissue specimens; as an adjunctive computer-assisted methodology to assist in the acquisition and measurement of images from microscope slides of formalin-fixed, paraffin-embedded breast cancer tissue sections for the presence of amplified HER-2/*neu* gene and as an aid in determining HER-2/*neu* amplification status, in conjunction with optional manual visualization directly through the fluorescence microscope can be classified in class II with the establishment of special controls. FDA believes that class II special controls provide reasonable assurance of the safety and effectiveness of the device.

FDA has identified no direct risks to health related to use of automated FISH enumeration systems. However, failure of the system to perform as indicated, could lead to inaccurate results that could

result in misdiagnosis, inappropriate treatment and improper patient management. The measures FDA recommends to mitigate these risks are described in the guidance document, "Class II Special Controls Guidance Document: Automated Fluorescence *in situ* Hybridization (FISH) Enumeration Systems", which includes recommendations for performance validation and labeling.

In addition to the general controls of the act, this device type is subject to the following special controls: "Class II Special Controls Guidance Document: Automated Fluorescence *in situ* Hybridization (FISH) Enumeration Systems". Section 510(m) of the act provides that FDA may exempt a class II device from the premarket notification requirements under section 510(k) of the act, if FDA determines that premarket notification is not necessary to provide reasonable assurance of the safety and effectiveness of the device. FDA has determined premarket notification is necessary to provide reasonable assurance of the safety and effectiveness of the device and, therefore, the device is not exempt from the premarket notification requirements. Thus, persons who intend to market this type device must submit to FDA a premarket notification submission containing information on the Automated Fluorescence *in situ* Hybridization (FISH) Enumeration Systems they intend to market prior to marketing the device.

A notice announcing this classification order will be published in the **Federal Register**. A copy of this order and supporting documentation are on file in the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852 and are available for inspection between 9 a.m. and 4 p.m., Monday through Friday.

As a result of this order, you may immediately market this device, subject to the general control provisions of the act and the special controls identified in this order. If you have any questions concerning this classification order, please contact Maria Chan at (240) 276-0493 ext. 130.

Sincerely yours,

Steven Gutman, M.D.

Steven I. Gutman, M.D., M.B.A.
Director
Office of *In Vitro* Diagnostic Device
Evaluation and Safety
Center for Devices and Radiological Health

510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:
k041875

B. Purpose for Submission:
New device

C. Analyte:
Her2/neu gene copy number on formalin-fixed paraffin-embedded breast cancer specimens

D. Type of Test:
Computer-assisted image analyzer for fluorescence in situ hybridization (FISH)

E. Applicant:
Vysis, Inc.

F. Proprietary and Established Names:
Vysis® AutoVysion™ System for PathVysion HER-2 DNA Kit

G. Regulatory Information:

1. Regulation section:
   21 CFR 866.4700, Automated Fluorescent in situ Hybridization (FISH) Enumeration Systems
2. Classification:
   II
3. Product Code:
   NTH, System, Automated Scanning Microscope and Image Analysis for fluorescence in situ hybridization (FISH) assays
4. Panel:
   Immunology 82

H. Intended Use:

1. Intended Use:
   The Vysis® AutoVysion™ System is an automated scanning microscope and image analysis system. It is intended for *in vitro* diagnostic use with the Vysis® PathVysion® HER-2 DNA Probe Kit to aid in the detection and enumeration of FISH signals in interphase nuclei, and to determine the LSI® HER-2 to CEP® 17 signal ratio of the HER-2/*neu* gene via FISH in formalin-fixed, paraffin-embedded human breast cancer tissue specimens. The AutoVysion System is intended to reduce overall hands-on time by performing automated enumeration. For a small percentage of samples (less than 7%) manual enumeration may be required.

   The Vysis® AutoVysion™ System is an adjunctive computer-assisted methodology to assist in the acquisition and measurement of images from microscope slides of formalin-fixed, paraffin-embedded breast cancer tissue sections for the presence of amplified HER-2/*neu* gene. The Vysis®

AutoVysion™ System is intended for use as aid in determining HER-2/*neu* amplification status, in conjunction with optional manual visualization directly through the fluorescence microscope.

2. Indication(s) for use:
When used with the Vysis® PathVysion® HER-2 DNA Probe Kit, the Vysis® AutoVysion™ System is indicated for use as
   a) an adjunct to existing clinical and pathologic information currently used as prognostic factors in stage II, node-positive breast cancer patients
   b) an aid to predict disease-free and overall survival in patients with stage II, node positive breast cancer treated with adjuvant cyclophosphamide, doxorubicin and 5-fluorouracil (CAF) chemotherapy; and,
   c) aid in the assessment of patients for whom HERCEPTIN® (Trastuzumab) treatment is being considered (see HERCEPTIN package insert).
3. Special condition for use statement(s):
For prescription use.
4. Special instrument Requirements:
Vysis® AutoVysion™ System

I. Device Description:

The Vysis® AutoVysion™ System consists of an automated fluorescence microscope with motorized scanning stage, a large format monochrome CCD camera, computer and scanning and assay specific analysis software. The microscope is equipped with a mercury arc lamp for fluorescence epi-illumination; three single-pass fluorescence filter sets for DAPI, SpectrumGreen™ (SG) and SpectrumOrange™ (SO) and a triple-pass fluorescence filter set for DAPI/SG/SO, all mounted in a motorized filter turret; 10x and 40x objectives in a motorized objective turret; 10x eyepieces; a CCD camera; and a motorized scanning stage that holds up to 8 slides. Images of single fluorescence colors are captured by the CCD camera and transferred to the computer. All functions are controlled by the System software.

J. Substantial Equivalence Information:

1. Predicate device name(s)
None
2. Predicate K number(s):
None
3. Comparison with predicate:
Not applicable

K. Standard/Guidance Document Referenced (if applicable):

FDA guidance documents on software validation and off-the shelf Software use and NCCLS- EP9-A2.

L. Test Principle:

A qualified user visually inspects the tumor regions of the slide, previously identified by a pathologist, identifies areas of tumor invasion with acceptable hybridization quality and records the coordinates of those areas for analysis through a point and

click interface. Once the target areas have been identified, the AutoVysion™ System enters a fully automatic process, capturing extended-focus images of the marked areas at 40x magnification in each color: DAPI. SpectrumGreen and SpectrumOrange. All image data is saved to disk. The hybridization signals in each area are detected and enumerated automatically. The slide is also assessed for appropriate hybridization quality requirements that, if not satisfied, the sample may be rejected for automatic analysis. Final review and reporting of sample results is performed by a qualified user.

The system uses a "targeted tiles" method for sampling the tumor. In this method, each field of view (FOV) in the area selected for analysis is sampled by placing a set of non-overlapping square "tiles" of equal size on the image. Each tile is comparable in size to the area of a tumor cell nucleus. The tiles are placed one by one in a way that maximizes the DAPI fluorescence contained in each tile, so that the set of tiles covers much of the nuclear material in the FOV. The spot count of a particular tile comprises the total spot count of the cell nuclei that are wholly or partly incorporated in the tile randomly reduced by truncation by tile boundary and microtome slicing. The method used to analyze the observed distribution of per-tile spot counts is the Expectation Maximization Algorithm (EM). EM is used to fit a mixture of two distributions to the observed two dimensional spot count distribution. The goodness of fit of the two-distribution model is compared with the goodness of fit of a single distribution to ensure that truly homogeneous samples are not erroneously fitted by two separate distributions. The HER-2/CEP 17 ratio is obtained directly from the parameters of the fitted distribution(s).

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

   a. *Precision/Reproducibility:*

   The Vysis® AutoVysion™ System was evaluated for inter-site and day-to-day reproducibility at 3 clinical sites. The study consisted of a total of 36 specimen slides prepared from four human breast tissue specimens with varying levels of HER-2/*neu* gene amplification (one normal, one borderline, one moderate and one high amplification). Each site received three of each of the specimens randomized over three days. The optimal number of fields of view (FOV) was determined using 5, 7 and 10 fields of view. All three numbers of FOVs gave similar results. The ten FOVs were selected to be used for all precision studies.

   Day-to-day reproducibility was determined by calculating the mean observed ratio of LSI HER-2/*neu* to CEP 17, standard deviation (SD) and percent coefficient of variation (%CV) generated from 10 fields of view for each specimen across the three study days. The p-values associated with the Levene test statistics were calculated to test the homogeneity of day-to-day variances, with a 0.05 significance level.

Results showed no statistically significant differences (see table below).

Expected	Observed ratios of LSI HER-2/*neu* to CEP 17									P-value
	Day 1			Day 2			Day 3			
	Mean	SD	%CV	Mean	SD	%CV	Mean	SD	%CV	
1.33	1.17	0.33	28.04	1.11	0.14	12.3	1.14	0.06	5.12	0.1152
1.71	2.08	0.61	29.34	2.38	0.64	26.82	2.45	NR	NR	0.9049
8.14	5.70	0.86	15.01	5.55	0.33	5.87	5.47	0.66	12.09	0.2788
12.97	6.42	0.81	12.55	7.42	0.17	2.24	8.01	0.35	4.38	0.1205

NR= No result

Inter-site reproducibility was similarly determined across the three study sites. Results for the three sites were not statistically significant and are summarized in the following table:

Expected	Observed ratios of LSI HER-2/*neu* to CEP 17									P-value
	Site 1			Site 2			Site 3			
	Mean	SD	%CV	Mean	SD	%CV	Mean	SD	%CV	
1.33	1.24	0.26	21.09	1.05	0.05	4.52	1.14	0.18	15.97	0.1833
1.71	2.09	0.58	27.84	2.42	NR	NR	2.39	0.75	31.23	0.5436
8.14	5.41	0.58	10.70	5.88	0.06	1.02	5.44	0.88	16.12	0.1612
12.97	6.95	1.32	19.03	7.51	0.81	10.72	7.39	0.30	4.04	0.1665

NR= No result

b. *Linearity/assay reportable range:*
Not applicable.

c. *Traceability (controls, calibrators, or method):*
The analytical traceability of the system depends on the Vysis® PathVysion® HER-2 DNA Probe Kit. The AutoVysion™ System employs ProbeCheck control slides for every run to assess the accuracy of signal enumeration and to monitor the assay performance.

d. *Detection limit (functional sensitivity):*
Not applicable

e. *Analytical specificity*
The specificity of the test result is dependent on the analytical performance of the Vysis® PathVysion® HER-2 DNA Probe Kit.

f. *Assay cut-off:*
The assay cut-off of the test result is dependent on the analytical performance of the Vysis® PathVysion® HER-2 DNA Probe Kit.

2. Comparison studies:

a. *Method comparison with predicate device:*
The substantial equivalence studies were based on comparison to conventional manual microscopy performed in accordance with Vysis® PathVysion® HER-2 DNA Probe Kit.

Duplicate slides from each tumor were randomized and assayed with the Vysis® PathVysion® HER-2 DNA Probe Kit according to the

package insert instructions prior to shipment to the study sites. The randomized slides were enumerated by the standard and test method at each of the three study sites. Two hundred thirty-four clinical slides from 39 tumors with varying levels of HER-2/*neu* copy number were used in the study.

Concordance was evaluated as the agreement between manually enumerated and the calculated HER-2 to CEP 17 signal ratio and the Vysis® AutoVysion™ System produced HER-2 to CEP 17 signal ratio. Among all tissue specimens with informative results for both methods, 92.5% (196/212) were correctly classified. Positive agreement was 96.0% and negative agreement was 89.2%. If samples with results in the equivocal range i.e. HER-2 to CEP 17 signal ratios between 1.5 and 3.0 were excluded from the calculation, total agreement was 98.8% (169/171) with 100% positive agreement and 97.5% negative agreement.

	Manual							
Scanner	1.5	1.5-<2.0	2.0-<2.5	2.5-<3.0	3.0-<5.0	5.0-<10	≥10	Total
<1.5	77	2	0	0	0	0	0	79
1.5-<2.0	17	3	3	1	0	0	0	24
2.0-<2.5	7	0	2	1	0	1	0	11
2.5-<3.0	3	0	0	1	0	2	0	6
3.0-<5.0	1	0	0	1	5	19	20	46
5.0-<10	0	1	0	1	5	19	20	46
≥10	0	0	0	0	0	1	3	4
Total	105	6	8	8	21	37	27	212

There were two false positive results by the AutoVysion™ System. When these two samples were repeated six times manually and by the scanner, both methods gave positive results in five of the six repeats.

The average bias for the manual enumeration ratio range of 1.18 to 4.49 was determined according to NCCLS guideline EP9-A2 and found to be 0.472 (SD = 1.24). This bias value was 11.7% of the average manual enumeration ratio of 4.05 which met the acceptable error of ±15%. The bias and % of average increased throughout the range as presented in the following table

Enumeration Ratio Range	Average Bias	% Average Enumeration Ratio
0.19-1.17	0.296	7.29
1.18-4.39	0.472	11.66
4.42-21	-2.98	-73.4
Overall	-0.742	-18.26

b. Matrix comparison:
Not applicable

3. Clinical studies:

a. *Clinical sensitivity:*
The clinical sensitivity of the test system is dependent on the analytical performance of the Vysis® PathVysion® HER-2 DNA Probe Kit.

b. *Clinical specificity:*
The clinical specificity of the test system is dependent on the analytical performance of the Vysis® PathVysion® HER-2 DNA Probe Kit.

c. *Other clinical supportive data (when a and b are not applicable)*
Not applicable.

4. Clinical cut-off:
The clinical cut-offs of the test result is dependent on the analytical performance of the Vysis® PathVysion® HER-2 DNA Probe Kit.

5. Expected values/Reference range:
Expected values of HER-2/CEP 17 ratio were established on breast cancer tissue specimens from 524 breast cancer patients with the Vysis® PathVysion® HER-2 DNA Probe Kit. Based on a cut-off ratio of 2.0, 433 of the specimens were negative and 91 positive for HER-2/*neu* gene amplification. The distribution of the HER-2/CEP 17 ratios for the 433 non-amplified specimens is summarized below.

	Range		
Statistics	0.1-1.0	1.1-1.5	1.6-1.99
Mean	0.86	1.15	1.72
SD	0.14	0.13	0.11
N	185	226	22

The following table summarizes the distribution of HER-2/CEP 17 ratios for the 91 amplified specimens.

	Range		
Statistics	2.0-5.0	5.1-10.0	>10.0
Mean	3.35	7.39	12.77
SD	0.95	1.41	1.80
N	33	42	16

N. Instrument Name:
Vysis® AutoVysion™ System

O. System Descriptions:
See (H) Device Description.

1. Modes of Operation:
Semi-automated computer-assisted interpretation.
2. Software:
FDA has reviewed applicant's Hazard Analysis and software development processes for this line of product types: Yes
3. Sample Identification:

Slide identification is entered manually into the AutoVysion™ System before the slides are loaded into the instrument.

4. Specimen Sampling and Handling:
   The microscope slides to be examined are loaded onto the microscope stage of the AutoVysion™ System and the user records the coordinates of those areas for analysis through a point and click interface. Once the target areas have been identified, the AutoVysion™ System automatically captures images of the marked areas in each fluorescence color and enumerates the hybridization signals in each area. The system also rejects slide that failed hybridization quality requirements for automatic analysis.
5. Assay Types:
   Computer-assisted image analysis of fluorescence in situ hybridization signals in interphase nuclei of cells in formalin-fixed paraffin-embedded tissue.
6. Reaction Types:
   Fluorescent microscopy
7. Calibration:
   The AutoVysion™ instrument is factory calibrated. Monthly calibration checks with End Switches and Movements tests should be performed. To assess accuracy of signal enumeration by the instrument, laboratory-stained Vysis ProCheck slides are used for every staining run.
8. Quality Control:
   The accuracy of the system depends on the laboratory following the quality control instructions recommended in the labeling of the fluorescence *in situ* hybridization (FISH) assay kit associated with the AutoVysion™.

P. Other Supportive Instrument Performance Characteristics Data Not Covered In The "M. Performance Characteristics" Section Of The SE Determination Decision Summary.

Q. Conclusion:

The petition for Evaluation of Automatic Class III Designation for this device is accepted. The device is classified as Class II under regulation 21 CFR 866.4700 with special controls. The special control guidance document " Class II Special Controls Guidance Document: Automated Fluorescence *in situ* Hybridization (FISH) Enumeration Systems" is available at WWW.fda.cdrh..... and includes recommendations for performance validation and labeling

R. Other Supportive Device and Instrument Information

The sponsor clarified the instrument calculated the HER-2/CEP 17 signal ratios using the "targeted tile" and the Expectation Maximization Algorithm and the manual method calculated the ratios according to the PathVysion DNA Probe kit.

The sponsor provided line listings for the time per slide analysis to support the "reduced hands-on-time" claim. Results showed for samples with equivocal results, there was no time saving since these samples had to be rescored manually. The claim was modified to limit to samples with clear cut results.

The sponsor indicated that the VP 2000 Processor was used for slide specimen processing (deparaffinization, FISH pretreatment and staining) and the HYBrite instrument was used for co-denaturation and FISH hybridization processes. Validation protocol and data were provided. Results showed eight of ten specimens processed by the automated process (VP 2000/HYBrite) were within acceptable limit of 15% when the differences between HER-2/CEP 17 signal ratios were compared to the manual method. Nine of the ten samples had same classification as the manual method with respect to HER-2 gene amplification. Slide quality ratings were equivalent or better than those processed manually.

S. Administrative Information:

1. Applicant contact information:

   a. *Name of applicant*:
      Vysis, Inc.
   b. *Mailing address*:
      3100 Woodcreek Dr.
      Downers Grove, IL 60515
   c. *Phone #*:
      (630) 271-7101
   d. *Fax #*:
      (630) 271-7438
   e. *E-mail address (optional)*:
      lynda.hague@vysis.com
   f. *Contact*:
      Lynda Hague

2. Review documentation:
   a. All required administrative paperworks were included in the submission: Indications for Use statement, Truthful and Accurate statement and a 510(k) Summary.
   b. The instrument is manufactured by Meta Systems, GmbH at Robert-Bosch-Str.6, D-68804, Altlussheim, Germany (Establishment Registration No. 9680625).
   c. Joseph Jorgens, III of the Office of Science and Technology reviewed the software hazard analysis for this device. On August 20, 2004, a memo

was received by e-mail from Mr. Jorgens stating that the software for the AutoVysion™ system was acceptable.

d. Chronology

07/12/04	Received in OIVD
07/13/04	Assigned to EAM
08/25/04	Additional information request (emailed)
09/03/04	Additional information received (emailed)
09/06/04	Reassigned to MMC
09/20/04	Request for clarification of information received
09/21/04	Received additional information
09/27/04	NSE letter for de novo application
10/13/04	Classification letter for petition received

T. Reviewer Name and Signature:

Maria Chan Date
CDRH/OIVD/DIHD

was received by e-mail from Mr. Jorgens stating that the software for the AutoVysion™ system was acceptable.

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07/12/04	Received in OIVD
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09/20/04	Request for clarification of information received
09/21/04	Received additional information
09/27/04	NSE letter for de novo application
10/13/04	Classification letter for petition received

T. Reviewer Name and Signature:

Maria Chan 12/16/04

Maria Chan **Date**
CDRH/OIVD/DIHD

[redacted] per R. Fischer

VYSIS

October 12, 2004

OCT 13 2004

Document Mail Center (HFZ-401)
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

Attention: Dr. Maria Chan, OIVD (HFZ-440)

Re: 510(k) No. K041875, Vysis® AutoVysion™ System: Request for Evaluation of Automatic Class III Designation under 513(f)(2)

Dear Dr. Chan:

510(k) Number for NSE Finding:
Vysis, Inc., respectfully requests that Premarket Notification 510(k) No. K041875 be considered for a risk-based classification of the Vysis AutoVysion System. A "not substantially equivalent" (NSE) decision was rendered for 510(k) No. K041875 on October 1, 2004.

Statement of Cross-Reference to 510(k):
Vysis, Inc., hereby cross-references information contained in 510(k) No. K041875.

Classification being Recommended:
Vysis, Inc., believes the documentation presented in Premarket notification 510(k) No. K041875 is sufficient to substantiate an order classifying the Vysis AutoVysion System as a Class II device (general and special controls) pursuant to section 513 of the Federal Food, Drug and Cosmetic Act (the Act).

Potential Benefits:
The potential benefits derived from use of the device outweigh the possible risks associated with the use of the device when the device is used as intended. These benefits are summarized below:

> There are no known *direct* risks to patient health. However, failure of the Vysis AutoVysion System to perform as indicated or error in interpretation of results may lead to improper patient management, which includes misdiagnosis and

improper treatment. Use of Vysis AutoVysion System results to detect initial disease or recurrent disease, to assess disease prognosis, to predict disease free and overall survival in patients, or assess patient treatment regimen without consideration of other clinical factors could pose a risk.

For use of the Vysis AutoVysion System with the Vysis® PathVysion HER-2 DNA Probe Kit:

- A falsely low ratio determination, i.e., false negative, could contribute to a delay in accurately assessing disease prognosis in patients with stage II, node-positive breast cancer, failure to accurately predict disease-free and overall survival in stage II, node-positive breast cancer patients treated with adjuvant cyclophosphamide, doxorubicin, and 5-fluorouracil (CAF) chemotherapy, or a failure to accurately assess patients for whom HERCEPTIN® (Trastuzumab) treatment is being considered.
- A falsely high ratio determination; i.e., a false positive, could contribute to failure to accurately assess disease prognosis in patients with stage II, node-positive breast cancer, failure to accurately predict disease-free and overall survival in stage II, node-positive breast cancer patients treated with adjuvant cyclophosphamide, doxorubicin, and 5-fluorouracil (CAF) chemotherapy, or inappropriately recommending HERCEPTIN® (Trastuzumab) treatment.

Proposed General and Special Controls:

Vysis, Inc., believes that general controls and special controls in accordance with FDA's draft Class II Special Control Guidance Document: "Fluorescence in situ Hybridization (FISH) Automated Enumeration Systems" constitute adequate information to ensure reasonable assurance of the safety and effectiveness of the Vysis AutoVysion System and 510(k) No. K041875, via the Premarket notification process 21 CFR 807. These controls parallel the safety and effectiveness information provided in 510(k) No. K041875 for its intended use. A proposed draft guidance document using FDA's template for Class II Special Controls Guidance Document is provided in Attachment 2 of this request to facilitate FDA's development of a guidance document.

We believe that the information provided with this request together with the information provided in 510(k) No. K041875 provide sufficient information to allow the Agency to conclude the device is reasonably likely to be safe and effective for its intended use.

Thank you in advance for your consideration of our request. If you have questions regarding this submission, please do not hesitate to contact Lynda Hague, the official contact for this submission at (630) 271-7101, FAX (630) 271-~~7438~~, or email (lynda.hague@vysis.com), or me at (630) 271-7070.

Sincerely,

Rolland D. Carlson, Ph.D.
General Manager, Divisional Vice President
Vysis Inc.
3100 Woodcreek Drive
Downers Grove, IL 60515

Attachment:

Proposed Draft Class II Special Controls Guidance Document: Fluorescence *in situ* Hybridization (FISH) Automated Enumeration Systems.

Reader's Copy via email and express mail to:

Maria M. Chan, Ph.D., DABMLI
Division of Immunology, Hematology and Pathology Devices (HFZ-440)
Office of In Vitro Diagnostic Device Evaluation and Safety
Center for Devices and Radiological Health
Food and Drug Administration
2098 Gaither Road
Rockville, MD 20850

[redacted]

Attachment 1

Proposed Draft Class II Special Controls Guidance Document: Fluorescence *in situ* Hybridization (FISH) Automated Enumeration Systems

Guidance for Industry and FDA Staff

Class II Special Controls Guidance Document: Fluorescence *in situ* Hybridization (FISH) Automated Enumeration Systems

Document issued on: DRAFT

For questions regarding this document contact XXXX at 301-594-XXXX ext. XXX or by email at XXXX.

C·D·R·H
Center for Devices and Radiological Health

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Division of Immunology, Pathology and Hematology Devices
Office of In Vitro Diagnostic Device Evaluation and Safety

Preface

Public Comment:

Comments and suggestions may be submitted at any time for Agency consideration to Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. Alternatively, electronic comments may be submitted to http://www.fda.gov/dockets.ecomments. When submitting comments, please refer to Docket No. XX. Comments may not be acted upon by the Agency until the document is next revised or updated.

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Contains Nonbinding Recommendations

Guidance for Industry and FDA Staff

Class II Special Controls Guidance Document: Fluorescence *in situ* Hybridization (FISH) Automated Enumeration Systems

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

1. Introduction

This guidance document was developed as a special controls guidance to support the classification of Fluorescence *in situ* Hybridization (FISH) Automated Enumeration Systems into class II (special controls). Fluorescence *in situ* Hybridization (FISH) Automated Enumeration Systems are devices consisting of an automated scanning microscope and image analysis system designed to detect and enumerate FISH signals in interphase nuclei. The systems are comprised of common hardware and software platforms with customized software applications for specific FISH assays. They are intended for *in vitro* diagnostic use with Fluorescence *in situ* Hybridization (FISH) assays as an aid in the detection, counting and classification of cells of clinical interest based on recognition of cellular objects of particular color, size and shape. The use of automated systems may reduce hands-on time compared to manual enumeration of FISH assays. The scope of this guidance document is limited to legally-marketed FISH assays.

This guidance is issued in conjunction with a Federal Register notice announcing the classification of Fluorescence *in situ* Hybridization (FISH) Automated Enumeration Systems.

Any firm submitting a premarket notification (510(k)) for a Fluorescence *in situ* Hybridization (FISH) Automated Enumeration System will need to address the issues covered in this special control guidance document. However, the firm need only show

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that its device meets the recommendations of the guidance or in some other way provides equivalent assurances of safety and effectiveness.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidance documents describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance documents means that something is suggested or recommended, but not required.

The Least Burdensome Approach

The issues identified in this guidance document represent those that we believe need to be addressed before your device can be marketed. In developing the guidance, we carefully considered the relevant statutory criteria for Agency decision-making. We also considered the burden that may be incurred in your attempt to comply with the statutory and regulatory criteria in the manner suggested by the guidance and in your attempt to address the issues we have identified. We believe that we have considered the least burdensome approach to resolving the issues presented in the guidance document. If, however, you believe that there is a less burdensome way to address the issues, you should follow the procedures outlined in the "**A Suggested Approach to Resolving Least Burdensome Issues**" document. It is available on our Center web page at: http://www.fda.gov/cdrh/modact/leastburdensome.html.

2. Background

FDA believes that special controls, when combined with the general controls, will be sufficient to provide reasonable assurance of the safety and effectiveness of a Fluorescence *in situ* Hybridization (FISH) Automated Enumeration System. A manufacturer who intends to market a device of this generic type should (1) conform to the general controls of the Federal Food, Drug, and Cosmetic Act (the Act), including the premarket notification requirements described in 21 CFR 807 Subpart E, (2) address the specific risks to health associated with an Fluorescence *in situ* Hybridization (FISH) Automated Enumeration System identified in this guidance and, (3) obtain a substantial equivalence determination from FDA prior to marketing the device.

This guidance document identifies the classification regulation and product code for a Fluorescence *in situ* Hybridization (FISH) Automated Enumeration System (Refer to **Section 4 – Scope**). In addition, other sections of this guidance document identify the risks to health and describe measures that, if followed by manufacturers and combined with the general controls, will generally address the risks associated with these Fluorescence *in situ* Hybridization (FISH) Automated Enumeration Systems and lead to a timely premarket notification [510(k)] review and clearance. This document supplements other FDA documents regarding the specific content requirements of a premarket notification submission. You should also refer to 21 CFR 807.87 and other FDA documents on this topic, such as the **510(k) Manual - Premarket Notification: 510(k) -**

Regulatory Requirements for Medical Devices,
http://www.fda.gov/cdrh/manual/510kprt1.html .

As explained in "**The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications; Final Guidance**[1]," a manufacturer may submit either a Traditional 510(k) or an Abbreviated 510(k). FDA believes an Abbreviated 510(k) provides the least burdensome means of demonstrating substantial equivalence for a new device, particularly once FDA has issued a guidance document that provides recommendations on what should be addressed in a submission for the device. Alternatively, manufacturers considering modifications to their own cleared devices may lessen the regulatory burden by submitting a Special 510(k).

3. The Content and Format of an Abbreviated 510(k) Submission

An Abbreviated 510(k) submission must include the required elements identified in 21 CFR 807.87, including the proposed labeling for the device sufficient to describe the device, its intended use, and the directions for its use. In an Abbreviated 510(k), FDA may consider the contents of a summary report to be appropriate supporting data within the meaning of 21 CFR 807.87(f) or (g); therefore, we recommend that you include a summary report. The report should describe how this guidance document was used during the device development and testing and the methods or tests used. The report should also include a summary of the test data or description of the acceptance criteria applied to address the risks identified in this document, as well as any additional risks specific to your device. This section suggests information to fulfill some of the requirements of 807.87 as well as some other items that we recommend you include in an Abbreviated 510(k).

Coversheet

The coversheet should prominently identify the submission as an Abbreviated 510(k) and cite the title of this guidance document.

Proposed labeling

Proposed labeling should be sufficient to describe the device, its intended use, and the directions for its use. (Refer to Section 8 for specific information that you should include in the labeling for this type of device.)

Summary report

We recommend that the summary report contain the following:

- A description of the device and its intended use. We recommend that the description include a complete discussion of the performance specifications and, when appropriate, detailed, labeled drawings of the device. You should also submit an "indications for use" enclosure.[2]

- A description of device design.
- Identification of the Risk Analysis method(s) used to assess the risk profile in general as well as the specific device's design and the results of this analysis. (Refer to Section 5 for the risks to health generally associated with the use of this device.)
- A discussion of the device characteristics that address the risks identified in this class II guidance document, as well as any additional risks identified in your risk analysis.
- A brief description of the test method(s) you have used or intend to use to address each performance aspect identified in Sections 6 and 7 of this guidance document. If you follow a suggested test method, you may cite the method rather than describing it. If you modify a suggested test method, you may cite the method but should provide sufficient information to explain the nature of and reason for the modification. For each test, you may either (1) briefly present the data resulting from the test in clear and concise form, such as a table, **or** (2) describe the acceptance criteria that you will apply to your test results.[3] (See also 21 CFR 820.30, Subpart C - Design Controls for the Quality System Regulation.)
- If you choose to rely on a recognized standard for any part of the device design or testing, you may include either: (1) a statement that testing will be conducted and meet specified acceptance criteria before the product is marketed, or (2) a declaration of conformity to the standard.[4] Because a declaration of conformity is based on results from testing, we believe you cannot properly submit a declaration of conformity until you have completed the testing the standard describes. For more information, please refer to section 514(c)(1)(B) of the Act and the FDA guidance, **Use of Standards in Substantial Equivalence Determinations; Final Guidance for Industry and FDA,** http://www.fda.gov/cdrh/ode/guidance/1131.html.

If it is not clear how you have addressed the risks identified by FDA or additional risks identified through your risk analysis, we may request additional information about aspects of the device's performance characteristics. We may also request additional information if we need it to assess the adequacy of your acceptance criteria. (Under 21 CFR 807.87(l), we may request any additional information that is necessary to reach a determination regarding substantial equivalence.)

As an alternative to submitting an Abbreviated 510(k), you can submit a Traditional 510(k) that provides all of the information and data required under 21 CFR 807.87 and described in this guidance. A Traditional 510(k) should include all of your methods, data, acceptance criteria, and conclusions. Manufacturers considering modifications to their own cleared devices should consider submitting Special 510(k)s.

The general discussion above applies to any device subject to a special controls guidance document. The following is a specific discussion of how you should apply this special controls guidance document to a premarket notification for a Fluorescence *in situ* hybridization enumeration system.

4. Scope

The scope of this document is limited to the following devices as described in 21 CFR 866.XXXX (product code: XXX):

21 CFR-866.XXXX:

5. Risks to Health

There are no known *direct* risks to patient health. However, failure of the test to perform as indicated or error in interpretation of results may lead to improper patient management, which includes misdiagnosis and improper treatment. Therefore, use of assay results to adjust a treatment regimen without consideration of other clinical factors could pose a risk. A falsely low fluorescence signal count, or false negative, could contribute to a delay in detecting the disease, disease recurrence, disease prognosis, or a false indication of response to therapy. A falsely high fluorescence signal count, or false positive, could contribute to unnecessary monitoring, inappropriate treatment decisions, or failure to treat adequately.

In the table below, FDA has identified the risks to health generally associated with the use of a Fluorescence *in situ* Hybridization (FISH) Automated Enumeration System addressed in this document. The measures recommended to mitigate these identified risks are described in this guidance document, as shown in the table below. You should conduct a risk analysis, prior to submitting your premarket notification, to identify any other risks specific to your device. The premarket notification should describe the risk analysis method. If you elect to use an alternative approach to address a particular risk identified in this document, or have identified risks additional to those in this document, you should provide sufficient detail to support the approach you have used to address that risk.

Identified risk	Recommended mitigation measures
Improper Patient Management	Sections 6, 7, & 8

6. Performance Characteristics

General Study Recommendations

We recommend that you include in the 510(k) a description of the FISH method used to detect the disease or condition of interest. You should also include a description of the

reagent components in the FISH kit. For the preclinical performance studies described below, we recommend that whenever possible, you include patient samples derived from the intended use population (e.g., breast cancer patients). Where not possible, spiked normal samples or samples derived from representative of positive and negative cultured cells can be used, however, we caution against using spiked or cultured cell samples as the only matrix in the evaluations, because they may not provide an accurate assessment of the performance characteristics. Clinical studies should include patient samples derived from the intended use population (e.g., breast cancer patients) and from appropriate control groups.

FDA recommends that you evaluate the assay in at least three external sites. Generally, you should assess performance in the testing environment where the device will ultimately be used (i.e., central laboratory) by individuals who will use the test in clinical practice. You should initially analyze data separately to evaluate any inter-site variation and include results of the analysis in the 510(k) summary report. It may be appropriate to report pooled results from the individual sites in the package insert if you can demonstrate that there are no significant differences in the results among sites. Before initiating a clinical study, you may wish to contact the Division of Immunology, Hematology and Pathology Devices.

We recommend that you provide appropriate specifics concerning protocols so that FDA can interpret acceptance criteria or data summaries during the review. For example, when referring to NCCLS protocols or guidelines, we recommend that you indicate which specific aspects of the protocols or guidelines you followed. We also recommend that you include protocol specifics in labeling, as these may be necessary to aid users in interpreting information in your labeling.

Software Validation

You should provide documentation of the software validation for all programs associated with the device. FDA guidances, "**Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices; Final,**" www.fda.gov/cdrh/ode/57.html and "**Guidance for Off-the-Shelf Software Use in Medical Devices; Final,**" www.fda.gov/cdrh/ode/1252.html contain information about the documentation recommended.

FDA believes the software used in class II Fluorescence *in situ* Hybridization (FISH) Automated Enumeration System devices meets the definition given in these guidance documents for devices with a minor or moderate level of concern, depending on the impact that the software application would have on the diagnosis, because they are used in the diagnosis of a condition which, if misdiagnosed, could result in no injury or non-serious injury to the patient. Therefore, you should provide documentation for the appropriate level of concern of the device.

Specific Performance Characteristics

Reproducibility

We recommend that you characterize within-run, day-to-day and site-to-site reproducibility of your device. FDA recommends using patient samples to assess reproducibility where possible. Cultured cell samples that contain a known quantity of representative positive and negative cells may also be used to supplement the studies. The samples should cover a range that is appropriate for your device. You should also evaluate reproducibility at relevant cell counts, including those near medical decision cut-off and near the limits of reportable range.

Where appropriate, we recommend that you include the items listed below in your analyses:

- sample types (e.g., formalin-fixed, paraffin-embedded breast cancer specimens)
- mean, standard deviation and coefficient of variation of within-run, day-to-day and site-to-site reproducibility
- sites at which the reproducibility protocol was run
- number of days, runs and observations

You should identify which factors were held constant, which were varied during the evaluation, and describe the computational methods or reference appropriate NCCLS standards.

Validation of Controls

A suitable control for use with the device should be identified and provided, if possible. Control samples to be used with the device should be developed and validated according to acceptable protocols. The controls should be representative of negative and positive (near the medical decision point) samples.

We recommend that you include the following items:

- types and levels of controls developed
- sample type (e.g. formalin-fixed, paraffin-embedded cultured cell lines)
- quantity of spiked cells in the sample, if applicable
- number of replicates tested
- expected values

7. Method Comparison

Because cell selection and enumeration systems may be based on different biological selection and detection agents, and because instrumentation may differ considerably between devices, FDA recommends that, for a Fluorescence *in situ* Hybridization (FISH)

Automated Enumeration System, you compare the results of your device to the reference used for the predicate device (i.e., the cleared or approved manual enumeration method). As with studies to evaluate performance characteristics, you may contact the Division of Immunology, Hematology and Pathology Devices for FDA input on your study plan prior to initiating comparison studies.

Clinical Studies

In order to demonstrate clinical equivalency to the manual enumeration method of the FISH assay, you should perform a clinical equivalency study to demonstrate that the selection and enumeration of fluorescent signals using your device is equivalent using a statistically-based method of analysis. You may demonstrate this by testing a suitable sample of patients and evaluating them by both the manual and automated enumeration methods, using NCCLS guidance document EP9-A, "Method Comparison and Bias Estimation using Patient Samples." Based on the protocol design, you should employ appropriate statistical tests to determine either sensitivity, specificity and concordance, or percent positive and percent negative and overall agreement. Any additional claims desired (e.g., reduced evaluation time as compared to manual evaluation) should be supported with clinical validation studies.

We recommend that you incorporate the following in your clinical evaluation study plan:

- Predicate device or reference method (gold standard comparisons)
- Patient specimens (inclusion/exclusion criteria, clinical status or diagnosis by what criteria, demographics and prevalence, type or sample size)
- We recommend that you have three or more investigators at separate sites, with one or more in the United States.
- Establish uniform protocols for external evaluation sites prior to the study. These should be followed consistently throughout the course of data collection. When changes are necessary, they should be documented and justified so that data can be properly interpreted.
- Studies should be performed using appropriate methods for quality control.
- Perform external evaluation studies under the review of an Institutional Review Board (IRB), when IRB oversight is required.
- Enroll patients using an approved informed consent form, or if using clinical specimens ensure that the appropriate consent was obtained, as required.

We recommend the following concerning sample size and selection:

- Sample size and method (e.g., inclusion and exclusion criteria) should be determined prior to beginning the clinical study. The sample size should have sufficient statistical power or ability to detect differences of clinical importance. Alternative approaches may be appropriate for a disease or condition having a low prevalence.

- You should adequately sample all clinical specimen matrices (e.g., formalin-fixed, paraffin-embedded breast cancer tissue) claimed in the intended use statement. We also recommend that you provide a clear description of how samples were selected, and whether samples were chosen to select for a specific clinical outcome or other characteristics.

Your 510(k) submission should include a description of your internal protocols and protocols for external evaluation studies, as well as study results. You should describe how you addressed the issues concerning study plan and sample selection listed above. We recommend that you include the following in the description of your results:

- Evaluate test data with analyses and conclusions by each investigator and pooled over investigators, if statistically and clinically justified.
- Describe the statistical methods you used.
- It may be helpful to include a summary of published information and/or clinical data pertinent to the device if you believe it supports your claims.

Presentation of results

When presenting the results of your study we recommend that you

- compare automated enumeration results obtained with your device to the reference method (e.g., manual enumeration), calculated in accordance with NCCLS EP9-A2, sections 4.1-8.3.
- stratify data and analyze by clinical status (e.g., positive or negative).
- determine either sensitivity, specificity and concordance, or percent positive and percent negative and overall agreement, as appropriate for your design.

8. Labeling

The premarket notification should include labeling in sufficient detail to satisfy the requirements of 21 CFR 807.87(e). The following suggestions are aimed at assisting you in preparing labeling that satisfies the requirements of 21 CFR 807.87(e).[5]

Directions for use

To meet the requirements of 21 CFR 807.87, you should provide clear and concise instructions that delineate the technological features of the specific device and how the device is to be used with slides prepared for FISH analysis. Instructions should require local/institutional training programs designed to familiarize users with the features of the device and how to use it in a safe and effective manner.

Limitations

We recommend that you provide limitations in labeling that describe what conditions may alter assay results.

Quality Control

To mitigate the risk of inaccurate results and to assist the user in verifying that the assay and equipment are performing properly, we recommend that you provide a description of quality control recommendations in the labeling.

Precautions and Warnings

We recommend that you emphasize in labeling that patient management and treatment decisions should not be made solely on the basis of results obtained with the device, but always in conjunction with other accepted methods of clinical assessment.

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[1] http://www.fda.gov/cdrh/ode/parad510.html

[2] Refer to http://www.fda.gov/cdrh/ode/indicate.html for the recommended format.

[3] If FDA makes a substantial equivalence determination based on acceptance criteria, the subject device should be tested and shown to meet these acceptance criteria before being introduced into interstate commerce. If the finished device does not meet the acceptance criteria and, thus, differs from the device described in the cleared 510(k), FDA recommends that submitters apply the same criteria used to assess modifications to legally marketed devices (21 CFR 807.81(a)(3)) to determine whether marketing of the finished device requires clearance of a new 510(k).

[4] See Required Elements for a Declaration of Conformity to a Recognized Standard (Screening Checklist for All Premarket Notification [510(K)] Submissions), http://www.fda.gov/cdrh/ode/reqrecstand.html.

[5] Although final labeling is not required for 510(k) clearance, final labeling must comply with the requirements of 21 CFR 801 or 21 CFR 809.10 before a medical device is introduced into interstate commerce. Labeling recommendations in this guidance are consistent with the requirements of part 801 and section 809.10.